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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	: 09/383,054	Confirmation No.	: 6042
Applicant	: David A. Edwards and Jeffrey S. Hrkach		
Filed	: August 25, 1999		
TC/A.U.	: 1615		
Examiner	: Amy E. Pulliam		
Docket No.	: 2685.1003-001		
Customer No.	: 000038421		
Title	: Stable Spray-Dried Protein Formulations		

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SUPPLEMENTAL APPEAL BRIEF

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Sir:

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(1) The Real Party of Interest

The real party of interest in this appeal is Advanced Inhalation Research, Inc. by virtue of the Assignment recorded on November 1, 1999 at Reel 010349 and frame 0126.

(2) Related Appeals and Interferences

There are no related appeals or interferences at this time known to the appellant, the assignee or its representative which will directly affect or be directly affected by or have a bearing in the Board's decision in the pending appeal.

(3) Status of the Claims

Claims 50, 52-69, 91, 93-108, and 128-131 are pending, finally rejected and appealed. Claims 1-49, 51, 70-90, 92 and 109-127 have been canceled.

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(5) Summary of the Invention

The invention relates to methods for producing spray-dried particles having improved stability of a protein comprising combining a protein, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and spray-drying the mixture to produce spray-dried particles comprising a stabilized protein. In Claim 50, for example, the particles consist of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

(6) Issues

The issue on appeal is whether the examiner has established a prima facie case of obviousness over Durrani.

(7) Grouping of Claims

Claims 53, 56, 57, 62-64, 94, 97, 98, 102-104 and 128-131 do not stand or fall together with the remaining claims.

(8) Argument

(a) The Rejection

All claims stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Durrani *et al.* ("Durrani). In support of the rejection the Examiner states:

> Durrani discloses a process to directly spray dry a drug/lipid powder composition comprising preparing an aqueous solution containing a drug and a lipid containing ethanol solution. The mixture is then spray dried to get particles (p 40, claim 1). Durrani further teach that the drug may be selected from a group which includes insulin.... Durrani further teaches that the lipid may be selected from the group consisting of phosphatidylglycerol.... Lastly, Durrani teach that the diameter of the resulting particles is between 0.1 and 20 microns (p 14, l 30)....
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> One of ordinary skill in the art would have been motivated to make a spray dried composition of a drug and a lipid based on the generic claim of Durrani. The expected result would be a stable spray dried powder formulation. Therefore, this invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

(b) The Rebuttal

The claims are directed to subject matter not embraced by the teachings of the cited reference. The present invention teaches methods for producing particles having properties and formulations neither disclosed nor suggested by Durrani.

According to MPEP §2142, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of skill in the art, to modify the reference or to combine the teachings of the reference to teach the invention. Second, there must be a reasonable expectation of success in practicing the invention.

Finally, the prior art reference must teach or suggest all the claim limitations. Durrani fails on all three criteria.

The present invention, as claimed, is directed to methods of producing protein containing particles in which the protein has improved stability. The particular problems associated with protein stability in aqueous solutions are described in the instant application. For example, the spray drying of proteins can result in materials that are thermally degraded upon processing. There can be a detrimental effect of protein degradation at the air-liquid interface of the droplets in the spray. The problems associated with protein stability can be solved by producing the protein particles according to the methods of the invention.

In contrast, Durrani is not concerned with, and does not address, the stability of any drug in any resulting spray-dried powder from Durrani's method. Even if it could be inferred that Durrani addresses the stability of the drug, Durrani does not address the stability of a protein drug in a resulting spray-dried powder. Durrani is simply not about a method for producing spray-dried particles comprising a stabilized protein or peptide wherein the particles consist of the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

Rather, Durrani is concerned with preparing drug/lipid powders effective to form liposomes with high drug encapsulation upon rehydration of the dried powder particles (page 4, lines 11-15). Therefore, the generic claim of Durrani provides no suggestion or motivation for the ordinarily skilled artisan to select the specific components (and only those components) of the claimed particles with improved protein stability. Given that Durrani contains no specific examples directed to particles containing proteins, the ordinarily skilled artisan does not have a reasonable expectation of success of producing protein particles with improved stability.

Durrani describes an improved method for direct spray-drying a drug/lipid composition to produce a powder which forms liposomes upon rehydration (ex vivo or in

vivo) that is essentially equivalent to that achieved by previous methods of spray-drying a drug/lipid composition which required the preformation of a liposome encapsulated drug suspension prior to spray-drying the liposome encapsulated drug suspension. Durrani teaches that the improved method alleviates the prior art need to preform liposome encapsulated drug suspensions while producing equivalent powders, and goes on to describe the ingredients and steps required to produce such powders. Therefore, there is no motivation or suggestion to use the methods of Durrani to overcome the obstacles involved with the spray-drying of proteins or which would direct the ordinarily skilled artisan to modify the cited generic claim to reach Appellants' claimed invention.

As discussed above, Durrani does not address any of the issues associated with protein stability, but rather describes a method of producing liposomes which is stated as having applicability to a range of therapeutics. The only working examples in Durrani teach particles which include, not a protein (or a peptide), but rather albuterol sulfate. Durrani never addresses the issue of protein stability, but rather, Durrani limits his teachings to a method for achieving the liposomal encapsulation of a drug. Therefore, the ordinarily skilled artisan searching for a method to produce particles with improved protein stability would not be provided a reasonable expectation of success in practicing the claimed methods by the teachings contained in the cited generic claim of Durrani.

The Examiner infers that improved protein stability is an inherent result of the methods of Durrani, stating that since "Durrani discloses the same components for the spray dried particles...that the protein integrity and tap density are inherent characteristics, and would be the same as those claimed by applicant...." However, the doctrine of inherency does not apply here where the prior art products are not "identical or substantially identical". *In re Best*, 195 USPQ 430 (CCPA 1977). The products *specifically* described by Durrani are directed to powders that do not contain proteins and contain additional components that facilitate liposome formation. The products *specifically* described by Durrani (which contain small organic molecules), by definition, cannot possess improved protein stability. Thus, the Examiner is applying the doctrine of

inherency, not to the products *specifically* described by Durrani, but those that fall within a broad generic disclosure. The doctrine of inherency simply does not reach products that are merely generically described. Indeed, the Examiner's position is wholly inconsistent with the long and accepted practice that improvement and selection inventions that fall within the generic disclosure of a reference can support a patent.

Further, Durrani fails to teach or suggest additional claim limitations. Claims 50, 52-69, 91, 93-108 and 128-131 are directed to a method for producing spray-dried particles having improved stability of a protein or peptide comprising combining a protein or peptide, a phospholipid and, optionally, a buffer salt and a co-solvent or an organic solvent, and spray drying the resulting mixture to produce spray-dried particles comprising a stabilized protein or peptide wherein the particles *consist of* the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent. The claims do not allow additional components.

Durrani is interested in a method for preparing a powder which, upon rehydration, yields liposome encapsulated drug at a comparable percent encapsulation to spray-dried preformed liposomes. All working examples presented in Durrani specifically teach particles which include, in addition to albuterol sulfate and lipid(s), other ingredients such as tocopherol, cholesterol and freon. Tocopherol is described as "a drug-protective and lipid-protective agent" (page 9, lines 20-21). These components are excluded from the present methods.

The Examiner dismisses this argument and relies upon the fact that Claim 1 of Durrani does not recite these additional excipients. Claim 1 requires that the composition contain a "lipid". The Examiner is reading more into this language than is there. It does not state that Durrani taught compositions which consist of protein and phospholipids and an optional buffer salt. The reference, taken as a whole, is plain in its teachings. Additional excipients that facilitate liposome formation are desired. There is no teaching

that good or even adequate results are obtained by eliminating all excipients that facilitate liposome formation.

As exemplified by Weiner *et al.* ("Liposomes as a Drug Delivery System", *Drug Development and Industrial Pharmacy,* 15(10): 1523-1554 (1989)) (enclosed herewith), the production and use of liposomes as a drug delivery system is a complex and distinct art -with its own unique concerns and obstacles. Weiner *et al.* describe the properties of liposomes, how liposomes are prepared and how they have been, and continue to be, adapted to efficiently and safely encapsulate a drug. Weiner *et al.* describe the various types of lipids that can be used to generate liposomes and the benefits and disadvantages of each (pages 1525-1529). Furthermore, Weiner *et al.* go on to state that "the internal or trapped volume and encapsulation efficiency greatly depends on liposomal content, lipid concentration, method of preparation and drug used" (page 1532, last paragraph). Weiner *et al.* teach the importance of the role of cholesterol in the formation of liposomes, the encapsulation of drugs and the resulting stability of the liposomes (page 1527, first paragraph). The teachings of Weiner are consistent with the teachings of Durrani, which stresses the importance of the types of lipids used in the formulation and the addition of drug and lipid containing agents such as cholesterol and tocopherol.

Thus, Durrani includes in its particles additional ingredients which materially affect the basic and novel characteristics of the claimed invention. Applicants respectfully submit that Durrani does not teach, suggest or recognize the possibility of preparing spray dried particles comprising a stabilized protein (or peptide) which consists of the protein, phospholipid and, optionally, the buffer salt of the present claims.

In Claims 128-131, a buffer salt is required. Durrani specifically states that "the aqueous solution be free of phosphate salts" (page 11, line 15). The particles of the claimed invention have no such restriction and can be prepared using phosphate salts (see Example 2). Indeed, such salts are required in Claims 128-131. Accordingly, the properties of the Durrani particles which necessitate that the aqueous solution be "phosphate free" simply do not exist in the particles of the instant invention and teaches away from the invention.

With respect to Claims 62-64 and 102-104, the claims require a specific range of tap densities. This too the Examiner asserts is generically taught by Durrani because Durrani does not teach any tap density at all and it is an inherent feature. Tap density is a physical characteristic of the powder. As can be seen from Durrani's examples, the physical characteristics change from run to run. Durrani's Table 2, for example, shows that some powders are sticky and some are free flowing. Example 1 of the present specification reports that the tap densities ranged between 0.02 and 0.2 g/cc. Clearly, it is not an inherent feature of the formulation alone. Thus, the Examiner's assertion is incorrect. There is no reason in Durrani to manufacture compositions with the specifically recited materials and the specifically recited tap densities. It is absurd for the Examiner to point to Durrani's failure to teach the claim limitation to support the rejection. Even if the Examiner asserts that all spray-dried products must inherently possess a tap density of less than 0.4 g/cc (Claim 62), the evidence of record clearly establishes that this is untrue of the lower tap densities. Thus, Claims 63, 64, 103 and 104 are separately patentable.

With respect to Claims 53 and 94, which limit the claims to human growth hormone, there is no motivation to specifically choose the formulation to consist essentially of hGH, a phospholipid (in an amount of at least about 10%) and an optional buffer salt, with an expectation of achieving good to excellent hGH stability. Certainly, the Examiner has pointed to none.

With respect to Claims 56, 57, 97, and 98, the specific stability to be achieved by the protein is recited. Obviously, Durrani does not teach this result. Further, the result is not an inherent feature of Durrani or spray drying as a whole. Thus, these claims are separately patentable.

(9) The Conclusion

In view of the fact that the Examiner has failed to establish a prima facie case of obviousness, Appellants request reversal of the rejection and allowance of the application.

Respectfully submitted,

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CLAIMS (last amended 5/14/03)

Claims 1-49 cancelled on 9/26/00, Claims 70-90 and 109-127, cancelled 10/18/01 and Claims 51 and 92, cancelled 5/14/03

50. Thrice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

52. The method of Claim 50 wherein the phospholipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols and combinations thereof.

53. The method of Claim 50 wherein the protein is human growth hormone.

54. The method of Claim 50 wherein the protein is present in the spray-dried particles in an amount ranging from about 1 to about 90 weight %.

55. The method of Claim 50 wherein protein stability is measured by SEC-HPLC.

56. The method of Claim 50 wherein the spray-dried particles retain at least about 70% protein integrity when stored at about 25°C and about 60% relative humidity conditions for six weeks.

57. The method of Claim 50 wherein the spray-dried particles retain at least about 50% protein integrity when stored at about 40°C and about 75% relative humidity conditions for six weeks.

58. The method of Claim 50 wherein the protein is a therapeutic, prophylactic or diagnostic agent.

59. (Amended) The method of Claim 50 wherein the solute concentration in said mixture is at least 0.1 weight/volume %.

60. The method of Claim 50 wherein the co-solvent includes an alcohol.

61. The method of Claim 50 wherein the organic solvent is present in the co-solvent in a concentration of at least 50 volume %.

62. The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.4 g/cm^3.

63. (Amended) The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.1 g/cm^3.

64. (Amended) The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.05 g/cm^3.

65. (Amended) The method of Claim 50 wherein the spray-dried particles have a median geometric diameter of between about 5 microns and about 30 microns.

66. (Amended) The method of Claim 50 wherein the spray-dried particles have an aerodynamic diameter of between about 1 micron and about 5 micron.

67. The particles produced by the method of Claim 50.

68. A method comprising administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of the spray-dried particles produced by the method of Claim 50.

69. (Thrice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and

b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

91. (Thrice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, an organic solvent, and optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

93. The method of Claim 91 wherein the phospholipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols and combinations thereof.

94. The method of Claim 91 wherein the protein is human growth hormone.

95. The method of Claim 91 wherein the protein is present in the spray-dried particles in an amount ranging from about 1 to about 90 weight %.

96. The method of Claim 91 wherein protein stability is measured by SEC-HPLC.

97. The method of Claim 91 wherein the spray-dried particles retain at least about 70% protein integrity when stored at about 25°C and about 60% relative humidity conditions for six weeks.

98. The method of Claim 91 wherein the spray-dried particles retain at least about 50% protein integrity when stored at about 40°C and about 75% relative humidity conditions for six weeks.

99. The method of Claim 91 wherein the protein is a therapeutic, prophylactic or diagnostic agent.

100. (Amended) The method of Claim 91 wherein the solute concentration in said mixture is at least 0.1 weight/volume %.

101. The method of Claim 91 wherein the solvent includes an alcohol.

102. The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.4 g/cm^3.

103. (Amended) The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.1 g/cm^3.

104. (Amended) The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.05 g/cm^3.

105. (Amended) The method of Claim 91 wherein the spray-dried particles have a median geometric diameter of between about 5 microns and about 30 microns.

106. (Amended) The method of Claim 91 wherein the spray-dried particles have an aerodynamic diameter of between about 1 micron and about 5 micron.

107. The particles produced by the method of Claim 91.

108. A method comprising administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of the spray-dried particles produced by the method of Claim 91.

128. (Twice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

129. (Twice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

130. (Twice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

131. (Twice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

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(a) The Rejection

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> One of ordinary skill in the art would have been motivated to make a spray dried composition of a drug and a lipid based on the generic claim of Durrani. The expected result would be a stable spray dried powder formulation. Therefore, this invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

(b) The Rebuttal

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According to MPEP §2142, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference itself or in the knowledge generally available to one of skill in the art, to modify the reference or to combine the teachings of the reference to teach the invention. Second, there must be a reasonable expectation of success in practicing the invention.

Finally, the prior art reference must teach or suggest all the claim limitations. Durrani fails on all three criteria.

The present invention, as claimed, is directed to methods of producing protein containing particles in which the protein has improved stability. The particular problems associated with protein stability in aqueous solutions are described in the instant application. For example, the spray drying of proteins can result in materials that are thermally degraded upon processing. There can be a detrimental effect of protein degradation at the air-liquid interface of the droplets in the spray. The problems associated with protein stability can be solved by producing the protein particles according to the methods of the invention.

In contrast, Durrani is not concerned with, and does not address, the stability of any drug in any resulting spray-dried powder from Durrani's method. Even if it could be inferred that Durrani addresses the stability of the drug, Durrani does not address the stability of a protein drug in a resulting spray-dried powder. Durrani is simply not about a method for producing spray-dried particles comprising a stabilized protein or peptide wherein the particles consist of the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

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Durrani describes an improved method for direct spray-drying a drug/lipid composition to produce a powder which forms liposomes upon rehydration (ex vivo or in

vivo) that is essentially equivalent to that achieved by previous methods of spray-drying a drug/lipid composition which required the preformation of a liposome encapsulated drug suspension prior to spray-drying the liposome encapsulated drug suspension. Durrani teaches that the improved method alleviates the prior art need to preform liposome encapsulated drug suspensions while producing equivalent powders, and goes on to describe the ingredients and steps required to produce such powders. Therefore, there is no motivation or suggestion to use the methods of Durrani to overcome the obstacles involved with the spray-drying of proteins or which would direct the ordinarily skilled artisan to modify the cited generic claim to reach Appellants' claimed invention.

As discussed above, Durrani does not address any of the issues associated with protein stability, but rather describes a method of producing liposomes which is stated as having applicability to a range of therapeutics. The only working examples in Durrani teach particles which include, not a protein (or a peptide), but rather albuterol sulfate. Durrani never addresses the issue of protein stability, but rather, Durrani limits his teachings to a method for achieving the liposomal encapsulation of a drug. Therefore, the ordinarily skilled artisan searching for a method to produce particles with improved protein stability would not be provided a reasonable expectation of success in practicing the claimed methods by the teachings contained in the cited generic claim of Durrani.

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Further, Durrani fails to teach or suggest additional claim limitations. Claims 50, 52-69, 91, 93-108 and 128-131 are directed to a method for producing spray-dried particles having improved stability of a protein or peptide comprising combining a protein or peptide, a phospholipid and, optionally, a buffer salt and a co-solvent or an organic solvent, and spray drying the resulting mixture to produce spray-dried particles comprising a stabilized protein or peptide wherein the particles *consist of* the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent. The claims do not allow additional components.

Durrani is interested in a method for preparing a powder which, upon rehydration, yields liposome encapsulated drug at a comparable percent encapsulation to spray-dried preformed liposomes. All working examples presented in Durrani specifically teach particles which include, in addition to albuterol sulfate and lipid(s), other ingredients such as tocopherol, cholesterol and freon. Tocopherol is described as "a drug-protective and lipid-protective agent" (page 9, lines 20-21). These components are excluded from the present methods.

The Examiner dismisses this argument and relies upon the fact that Claim 1 of Durrani does not recite these additional excipients. Claim 1 requires that the composition contain a "lipid". The Examiner is reading more into this language than is there. It does not state that Durrani taught compositions which consist of protein and phospholipids and an optional buffer salt. The reference, taken as a whole, is plain in its teachings. Additional excipients that facilitate liposome formation are desired. There is no teaching

that good or even adequate results are obtained by eliminating all excipients that facilitate liposome formation.

As exemplified by Weiner *et al.* ("Liposomes as a Drug Delivery System", *Drug Development and Industrial Pharmacy,* 15(10): 1523-1554 (1989)) (enclosed herewith), the production and use of liposomes as a drug delivery system is a complex and distinct art -with its own unique concerns and obstacles. Weiner *et al.* describe the properties of liposomes, how liposomes are prepared and how they have been, and continue to be, adapted to efficiently and safely encapsulate a drug. Weiner *et al.* describe the various types of lipids that can be used to generate liposomes and the benefits and disadvantages of each (pages 1525-1529). Furthermore, Weiner *et al.* go on to state that "the internal or trapped volume and encapsulation efficiency greatly depends on liposomal content, lipid concentration, method of preparation and drug used" (page 1532, last paragraph). Weiner *et al.* teach the importance of the role of cholesterol in the formation of liposomes, the encapsulation of drugs and the resulting stability of the liposomes (page 1527, first paragraph). The teachings of Weiner are consistent with the teachings of Durrani, which stresses the importance of the types of lipids used in the formulation and the addition of drug and lipid containing agents such as cholesterol and tocopherol.

Thus, Durrani includes in its particles additional ingredients which materially affect the basic and novel characteristics of the claimed invention. Applicants respectfully submit that Durrani does not teach, suggest or recognize the possibility of preparing spray dried particles comprising a stabilized protein (or peptide) which consists of the protein, phospholipid and, optionally, the buffer salt of the present claims.

In Claims 128-131, a buffer salt is required. Durrani specifically states that "the aqueous solution be free of phosphate salts" (page 11, line 15). The particles of the claimed invention have no such restriction and can be prepared using phosphate salts (see Example 2). Indeed, such salts are required in Claims 128-131. Accordingly, the properties of the Durrani particles which necessitate that the aqueous solution be "phosphate free" simply do not exist in the particles of the instant invention and teaches away from the invention.

With respect to Claims 62-64 and 102-104, the claims require a specific range of tap densities. This too the Examiner asserts is generically taught by Durrani because Durrani does not teach any tap density at all and it is an inherent feature. Tap density is a physical characteristic of the powder. As can be seen from Durrani's examples, the physical characteristics change from run to run. Durrani's Table 2, for example, shows that some powders are sticky and some are free flowing. Example 1 of the present specification reports that the tap densities ranged between 0.02 and 0.2 g/cc. Clearly, it is not an inherent feature of the formulation alone. Thus, the Examiner's assertion is incorrect. There is no reason in Durrani to manufacture compositions with the specifically recited materials and the specifically recited tap densities. It is absurd for the Examiner to point to Durrani's failure to teach the claim limitation to support the rejection. Even if the Examiner asserts that all spray-dried products must inherently possess a tap density of less than 0.4 g/cc (Claim 62), the evidence of record clearly establishes that this is untrue of the lower tap densities. Thus, Claims 63, 64, 103 and 104 are separately patentable.

With respect to Claims 53 and 94, which limit the claims to human growth hormone, there is no motivation to specifically choose the formulation to consist essentially of hGH, a phospholipid (in an amount of at least about 10%) and an optional buffer salt, with an expectation of achieving good to excellent hGH stability. Certainly, the Examiner has pointed to none.

With respect to Claims 56, 57, 97, and 98, the specific stability to be achieved by the protein is recited. Obviously, Durrani does not teach this result. Further, the result is not an inherent feature of Durrani or spray drying as a whole. Thus, these claims are separately patentable.

(9) The Conclusion

In view of the fact that the Examiner has failed to establish a prima facie case of obviousness, Appellants request reversal of the rejection and allowance of the application.

Respectfully submitted,

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CLAIMS (last amended 5/14/03)

Claims 1-49 cancelled on 9/26/00, Claims 70-90 and 109-127, cancelled 10/18/01 and Claims 51 and 92, cancelled 5/14/03

50. Thrice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

52. The method of Claim 50 wherein the phospholipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols and combinations thereof.

53. The method of Claim 50 wherein the protein is human growth hormone.

54. The method of Claim 50 wherein the protein is present in the spray-dried particles in an amount ranging from about 1 to about 90 weight %.

55. The method of Claim 50 wherein protein stability is measured by SEC-HPLC.

56. The method of Claim 50 wherein the spray-dried particles retain at least about 70% protein integrity when stored at about 25°C and about 60% relative humidity conditions for six weeks.

57. The method of Claim 50 wherein the spray-dried particles retain at least about 50% protein integrity when stored at about 40°C and about 75% relative humidity conditions for six weeks.

58. The method of Claim 50 wherein the protein is a therapeutic, prophylactic or diagnostic agent.

59. (Amended) The method of Claim 50 wherein the solute concentration in said mixture is at least 0.1 weight/volume %.

60. The method of Claim 50 wherein the co-solvent includes an alcohol.

61. The method of Claim 50 wherein the organic solvent is present in the co-solvent in a concentration of at least 50 volume %.

62. The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.4 g/cm^3.

63. (Amended) The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.1 g/cm^3.

64. (Amended) The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.05 g/cm^3.

65. (Amended) The method of Claim 50 wherein the spray-dried particles have a median geometric diameter of between about 5 microns and about 30 microns.

66. (Amended) The method of Claim 50 wherein the spray-dried particles have an aerodynamic diameter of between about 1 micron and about 5 micron.

67. The particles produced by the method of Claim 50.

68. A method comprising administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of the spray-dried particles produced by the method of Claim 50.

69. (Thrice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and

b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

91. (Thrice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, an organic solvent, and optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

93. The method of Claim 91 wherein the phospholipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols and combinations thereof.

94. The method of Claim 91 wherein the protein is human growth hormone.

95. The method of Claim 91 wherein the protein is present in the spray-dried particles in an amount ranging from about 1 to about 90 weight %.

96. The method of Claim 91 wherein protein stability is measured by SEC-HPLC.

97. The method of Claim 91 wherein the spray-dried particles retain at least about 70% protein integrity when stored at about 25°C and about 60% relative humidity conditions for six weeks.

98. The method of Claim 91 wherein the spray-dried particles retain at least about 50% protein integrity when stored at about 40°C and about 75% relative humidity conditions for six weeks.

99. The method of Claim 91 wherein the protein is a therapeutic, prophylactic or diagnostic agent.

100. (Amended) The method of Claim 91 wherein the solute concentration in said mixture is at least 0.1 weight/volume %.

101. The method of Claim 91 wherein the solvent includes an alcohol.

102. The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.4 g/cm^3.

103. (Amended) The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.1 g/cm^3.

104. (Amended) The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.05 g/cm^3.

105. (Amended) The method of Claim 91 wherein the spray-dried particles have a median geometric diameter of between about 5 microns and about 30 microns.

106. (Amended) The method of Claim 91 wherein the spray-dried particles have an aerodynamic diameter of between about 1 micron and about 5 micron.

107. The particles produced by the method of Claim 91.

108. A method comprising administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of the spray-dried particles produced by the method of Claim 91.

128. (Twice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

129. (Twice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

130. (Twice Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

131. (Twice Amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.